

Exhibit B

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Cancer symptoms and side effects : Graft versus host disease (GVHD)



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About graft versus host disease (GVHD)



This page tells you about graft versus host disease (GVHD). You can find out about

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What GVHD is

GVHD is a complication of a bone marrow or stem cell transplant from another person. This is a 'donor transplant'. Your doctor may call it an allogeneic (aloe-gen-ay-ik) transplant.

You can get GVHD whether your donor is a brother or sister (sibling) or is unrelated to you. The degree of GVHD a person can get varies a lot. Some people have a very mild form which doesn't last long. For others, GVHD can be severe. It may even be life threatening in a few cases. Some people may have GVHD over many months, even years (chronic GVHD).

GVHD means that the cells you got from your donor are attacking your own body cells. This happens because the donated cells (the graft) see your body cells (the host) as foreign, and mount an attack.

It is difficult to say who will develop GVHD. We don't know exactly, but somewhere between 1 and 4 out of every 5 people (20 to 80%) having a donor transplant will develop some degree of GVHD.

How GVHD develops

GVHD happens because the transplant affects your immune system. A bone marrow or stem cell transplant from another person means that their bone marrow cells are replacing yours.

Your bone marrow makes all your blood cells. T cells are white blood cells that help us fight infections. T cells attack and destroy cells they see as foreign, and potentially harmful, like bacteria and viruses. Normally T cells don't attack your own body cells, because they recognise proteins on the cells called HLA (human leukocyte antigens). We inherit our HLA from our parents. Apart from identical twins (who have the same HLA), it is unique to each person.

After a transplant your bone marrow starts making new blood cells.


These new blood cells are different from other cells in your body because the donor's HLA is not the same as yours. So the new T cells don't recognise your body cells as part of you, and may begin to attack them. This attack can affect different areas of your body. Most commonly, it affects the

- Skin
- Digestive system (including the bowel and stomach)
- Liver

Before a bone marrow or stem cell transplant, both you and your donor have blood tests to check how closely your HLA matches. This test is called tissue typing. The rule is

- A close HLA match means GVHD is less likely
- The more differences there are between your HLA and your donor's, the more likely you are to get GVHD

Possible benefits of GVHD

The symptoms of GVHD can be difficult to cope with, and in some cases GVHD is a serious, even life threatening, problem. But if you are having a transplant for leukaemia, having a small amount of GVHD may be a good thing. As well as attacking your body cells, the donor T cells will also attack any remaining leukaemia cells. Doctors call this the graft versus disease effect, or graft versus leukaemia effect (the 'graft' means the donor T cells). 

Risk factors for GVHD

There are a number of factors that can increase your risk of GVHD. These are

- Unrelated donor transplants
- Mismatched donors
- Age – the older you are, the greater your risk of developing GVHD
- Having a donor of a different sex to you
- Testing positive for cytomegalovirus (CMV)

If your donor is not related to you, your risk of developing GVHD is greater than if your donor is a brother or sister (sibling).

Your donor will be as close an HLA match as possible. But sometimes the best available bone marrow donor is still a slight mismatch. This increases the risk of GVHD.

If your donor is a different sex to you, the risk of GVHD is slightly increased. This is particularly true if a male has a female donor who has had children or been pregnant in the past.

Cytomegalovirus (pronounced sy-toe-meg-ah-vee virus), (CMV) is a very common virus that is usually harmless. Over 4 out of 10 people (40%) in the general population test positive for CMV. In other words, they have CMV antibodies in their blood. If you are CMV negative but your donor is positive, your risk of GVHD is higher.

Types of GVHD

GVHD is grouped according to when it starts after your transplant. It is either

- Acute GVHD – starts within 3 months of your transplant
- Chronic GVHD – starts at least 3 months after your transplant

Acute GVHD can be mild or severe. It will not start until your new bone marrow starts to make blood cells (doctors call this engraftment). This is usually about 2 to 3 weeks after your transplant. Acute GVHD often starts with a rash on the palms of your hands and soles of your feet. Or a rash on your face. Acute GVHD may also affect your gut and liver, as well as your skin. This can cause diarrhoea, nausea and yellowing of the skin (jaundice).

Chronic GVHD can follow acute GVHD or appear several months after your transplant, even if you've not had the acute form. But you are more likely to get chronic GVHD if you have had acute GVHD. Like acute GVHD it may affect your skin, gut, liver or mouth. But it can also affect other parts of your body, such as your eyes and lungs. Chronic GVHD may be mild or severe, and for some people can go on for several months, even years.

Why doctors don't always try to prevent GVHD

Doctors know more about how to prevent GVHD than they did when transplants were first used. But it is still a common complication of bone marrow and stem cell transplants.

In the past doctors tried to prevent GVHD as much as possible. But they noticed that although GVHD was reduced, the disease was more likely to come back (relapse). So nowadays doctors fine tune the treatments to prevent GVHD. They try to lower the risk of serious GVHD as far as possible, but still keep some benefits of GVHD. This may help to stop the disease coming back.

Chronic GVHD is also a problem because

- More matched unrelated and mismatched transplants are being done
- Doctors are now treating older people with less intensive mini transplants
- Donor lymphocyte infusion (DLI) for relapsed disease may be used

Mini transplants use stem cells rather than bone marrow. Using stem cells for allogeneic transplants may have a slightly increased risk of chronic GVHD. But the picture isn't entirely clear.

Nowadays doctors are able to treat people with diseases such as chronic myeloid leukaemia and myeloma, whose disease has come back after a donor transplant. They use a treatment called donor lymphocyte infusion (DLI), using white blood cells from the donor. The idea is that the donor's cells will attack the disease (the graft versus disease effect). But this is very likely to generate some GVHD. Indeed, doctors may try to bring about a small amount of GVHD as this shows that your donor's cells may be attacking your disease.

